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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	GHDX-005	5745

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35-38,40-47,51,52,59,60,62 and 64* is/are pending in the application.

4a) Of the above claim(s) *40 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35-38,41-47,51,52,59,60 and 62* is/are rejected.

7)☒ Claim(s) *31 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 12, 2009 has been entered.

Claims 31, 35-38, 40-47, 51-52, 59-60, 62, and 64 are currently pending.

Claims 31 and 60 have been amended.

Claims 40 and 64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 23, 2006.

Claim Objections

2. Claim 31 is objected to for having a typographical error. The word "and" should be deleted from the end of step (a).

Claims 60 is objected to because the claim recites RNA transcripts which have not been elected.

Claim Rejections - 35 USC § 112 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following are new rejections:

Claims 41-47, 51, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41-47 and 59 are rejected over the recitation of the phrase "the level of the LAMC2 RNA transcript" in claim 41. There is insufficient antecedent basis for this phrase in the claim because although the claims previously refer to "the normalized level of the LAMC2 RNA transcript" they do not refer to "the level of the LAMC2 RNA transcript".

Claim 51 is rejected over the recitation of the phrase "said cooled lysis solution" in claim 51. There is insufficient antecedent basis for this phrase in the claim because although the claim previously refers to "cooling the lysis solution" the claim does not refer to "a cooled lysis solution".

Claim Rejections - 35 USC § 112 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified:

Claims 31, 35-38, 41-47, 51-52, 59-60, and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

Claim 31 is drawn to a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an ErbB1 inhibitor. Claim 31 comprises (a) assaying a normalized level of a predictive RNA transcript in a sample comprising ErbB1 expressing colon cancer cells obtained from said patient wherein the predictive RNA transcript is the transcript of laminin gamma 2 (LAMC2); (b) analyzing the normalized level of the LAMC2 transcript; and (c) predicting the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript, wherein an increased normalized level of LAMC2 RNA transcript correlates with resistance of the colon

cancer to treatment with an ErbB1 inhibitor, wherein the ErbB1 inhibitor is erlotinib, cetuximab, or gefitinib. Thus the nature of the invention requires the knowledge of a reliable association between the level of LAMC2 in a sample and how a patient will respond to treatment with an ErbB1 inhibitor, specifically erlotinib, cetuximab, or gefitinib.

Scope of the Claims:

The claims are broadly drawn to method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an ErbB1 inhibitor wherein the ErbB1 inhibitor is erlotinib, cetuximab, or gefitinib. The claims require assaying a normalized level of a predictive RNA transcript, wherein the predictive RNA transcript is the transcript of laminin gamma 2 (LAMC2). According to Airenne (Cell Tissue Research 2000) there are two different LAMC2 transcripts and the two different LAMC2 transcripts are differentially expressed. Thus the instant claims encompass assaying a normalized level of either of the two LAMC2 transcripts.

Teachings in the Specification and Examples:

The specification (page 25) teaches that EGFR (also known as ErbB1) is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several ErbB1 inhibitors are promising drug candidates for the treatment of ErbB1 expressing cancers. The specification further teaches the following ErbB1 inhibitors: (i) Iressa (gefitinib) is a small synthetic quinazoline that competitively inhibits the ATP binding site of ErbB1 and has been in

Phase III clinical trials for the treatment of non-small-cell lung carcinoma; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12) has been shown to inhibit the proliferation and invasiveness of ErbB1 positive human breast cancer cells; (iii) Cetuximab is a monoclonal antibody that blocks the ErbB1 and ErbB1 -dependent cell growth that is currently being tested in phase III clinical trials; and (iv) Tarceva™ (erlotinib) which has shown promising indications of anti-cancer activity in patients with advanced ovarian cancer, and non-small cell lung and head and neck carcinomas.

The specification teaches (Example 2) that twenty-three colon adenocarcinoma patients in all were studied using a 192-gene assay. Following treatment with an unspecified EGFR inhibitor, three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. Table 3 shows the results obtained using the partial response criterion. LAMC2 was found to be over expressed. Specifically LAMC2 had a negative response and a p value of 0.0357. Here the term "negative" indicates that greater expression of the gene decreased likelihood of response to treatment with ErbB1 inhibitor, and "positive" indicates that increased expression of the gene increased likelihood of response to ErbB1 inhibitor (page 28). Table 4 shows the results analysis of colon cancer patient data using clinical benefit criteria. Here there is no data provided for LAMC2. Further with respect to claim 60 Table 4 shows that CD44v6 had a negative response and a p value of 0.0047.

In the instant case the specification does not teach which ErbB1 inhibitors were used. However it is noted for the record that the Applicants have submitted a declaration by Joffre B. Baker, PhD stating that the patients were treated with an ErbB1

inhibitor selected from erlotinib, gefitinib, cetuximab, EMD72000, and AEE788. Dr. Baker states that the results presented in tables 3 and 4 were the result of treatment with these EGFR inhibitors. However the Applicants have not provided data for each individual drug being claimed (erlotinib, cetuximab, or gefitinib). That is the declaration and specification as originally filed do not provide data which separately establish the level of LAMC2 mRNA in subjects showing a beneficial response to erlotinib, subjects showing a beneficial response to cetuximab, and subjects showing a beneficial response to gefitinib. In the instant case the specification (page 28) teaches that only 23 colon cancer patients were treated with an EGFR inhibitor and the declaration states that the patients were treated with one of five different EGFR inhibitors. Neither the specification nor the declaration state the number of patients treated with each drug or whether a partial response was observed for each of the drugs. Since the specification and declaration provide information regarding only the combination of patients treated with the 5 different drugs, the data cannot be interpreted in order to ascertain whether colon cancer patients with elevated levels of LAMC2 are actually less likely to respond to a treatment with an ErbB1 inhibitor.

Further it is noted that the specification only teaches an association between increased levels of NM_005562 (a single LAMC2 transcript) and the response to treatment with an ErbB1 inhibitor, yet the claims encompass a method of detecting the level of any LAMC2 transcript and making a prediction based on those levels. As noted above Airenne (Cell Tissue Research 2000) teaches that there are two different LAMC2 transcripts and the two different transcripts are differentially expressed.

State of the Art and the Unpredictability of the Art:

Further the art of determining if erlotinib, cetuximab, and gefitinib will each be less effective in patients with increased LAMC2 levels is highly unpredictable. The post filing date art of Giaccone teach six EGFR (also known as ErbB1) inhibitors (Iressa (gefitinib), Tarceva (erlotinib), lapatinib, cenertinib, ZD6474, and AEE788). Giaccone additionally teaches that each of these drugs has a different mechanism in which it acts on EGFR receptor. For example Iressa (gefitinib) and Tarceva (erlotinib) inhibit the tyrosine kinase of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR. These teachings are relevant to point out because the Applicants have not provided data for each individual drug being claimed (erlotinib, cetuximab, or gefitinib). That is the declaration and specification as originally filed do not provide data which separately establish the level of LAMC2 mRNA in subjects showing a beneficial response to erlotinib, subjects showing a beneficial response to cetuximab, and subjects showing a beneficial response to gefitinib. In the absence of a clear showing of an association between increased LAMC2 mRNA levels and a clinically beneficial response to each of the drugs erlotinib, cetuximab, or gefitinib, it remains unpredictable as to whether LAMC2 mRNA levels can be used to predict the likelihood of a beneficial response to these drugs particularly since each of the claimed drugs is present in a different class of EGFR inhibitors and has a different mechanism in which it acts on the EGFR receptor.

Additionally it is highly unpredictable if any LAMC2 transcript can be used to predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an ErbB1 inhibitor. As discussed above there are 2 different LAMC2 transcripts. The teachings of Airenne (Cell Tissue Research 2000) support this argument of unpredictability. Specifically Airenne teaches that when the laminin gamma 2* transcript expression pattern was compared with that of the gamma 2 chain, a similar tissue distribution was observed. There was however a significant difference in expression levels. The longer gamma 2 transcript was found to be much more abundant than the shorter gamma 2* variant. This is relevant to the instant application because it demonstrates that it is possible to obtain different results depending on the transcript being assayed.

Quantity of Experimentation:

The specification asserts that patients diagnosed with colon cancer with elevated levels of LAMC2 are less likely to respond to a treatment with an ErbB1 inhibitor. However the specification is silent as to which ErbB1 inhibitor was used. Therefore it is unclear if the claimed method would work for any ErbB1 inhibitor, specifically erlotinib, cetuximab, or gefitinib. Thus further experimentation would be required. For example, such experimentation may involve treating colon cancer patients with different types of ErbB1 inhibitors, namely erlotinib, cetuximab, or gefitinib and conducting multiple gene expression assays to determine the expression levels of LAMC2. Further these patients would have to be monitored to determine disease progression. Such random, trial by

error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

The claims are drawn to a method for predicting the likelihood that colon cancer patients will respond to treatment with erlotinib, cetuximab, or gefitinib by determining the normalized level of LAMC2. As discussed above, whether an association exists between increased levels of LAMC2 and the response to each of these drugs is highly unpredictable in the absence of a clear showing of an association between increased LAMC2 mRNA levels and a clinically beneficial response to each of the drug erlotinib, cetuximab, or gefitinib. Further the data in the specification is based on the expression of a single LAMC2 transcript yet the claims encompass detecting the expression level of

any LAMC2 transcript. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to Arguments

5. With regard to the objections, the Applicants argue that claim 60 recites a reasonable number of sequences for examination purposes (i.e. 10 sequences). Therefore this objection should be withdrawn. This argument has been fully considered but is not persuasive because claims to polynucleotide sequences are considered for independence, relatedness, distinction and burden as for claims to any other type of molecule. In the instant application each gene constitutes an independent and distinct invention within the meaning of 35 USC 121 since each gene consists of a different nucleotide sequence, has a different melting point, a different specificity of hybridization and encodes for a protein having a different biological activity. Therefore, with regard to claim 60 a search for multiple genes or multiple combinations of genes in addition to LAMC2 is an undue burden on the office. Therefore until claim 31 is found allowable, claim 60 will be objected to for reciting non elected RNA transcripts. Additionally it is noted for the record that if claim 31 is found allowable it does not necessarily mean that claim 60 will be allowable because the examiner will first have to consider if the specification provides enablement for each of the additional genes recited by claim 60.

Regarding the enablement rejection the Applicants argue that they have shown a negative correlation between LAMC2 levels and patient response to at least 3 classes of ErbB1 inhibitors they believe the claims are enabled for ErbB1 inhibitors in these classes, and specifically erlotinib, cetuximab, or gefitinib. This argument has been fully considered but is not persuasive. As stated in the previous office action the declaration and specification as originally filed do not provide data which separately establish the levels of LAMC2 mRNA in subjects showing a beneficial response to erlotinib, subjects showing a beneficial response to cetuximab and subjects showing a beneficial response to gefitinib. In the instant case the specification (page 28) teaches that 23 colon cancer patients were treated with an EGFR inhibitor and the declaration states that the patients were treated with one of five different EGFR inhibitors. Neither the specification nor the declaration state the number of patients treated with each drug or whether a partial response was observed for each of the drugs. Since the specification and declaration provide information regarding only the combination of patients treated with the 5 different drugs, the data cannot be interpreted in order to ascertain whether colon cancer patients with elevated levels of LAMC2 are actually less likely to respond to a treatment with each of the three claimed ErbB1 inhibitors. It would helpful if Applicants could provide if possible more information such as which drug each patient received and the expression level for each patient so that it can be determined if each drug is enabled.

Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634